Remarks

Claims 15 and 17 are under examination. Claims 1-14 were previously withdrawn from consideration and claim 16 was previously canceled without prejudice. Claims 15 is currently amended. Claim 17 has been cancelled herein without prejudice. Claims 18 and 19 have been added. Reconsideration is respectfully requested in view of the above claim amendments, the following remarks, and the Declaration of Renato V. Iozzo, M.D., under 37 C.F.R. 1.132, submitted herewith.

The specification has been amended by replacing the paragraph at page 19, lines 11-24 with an amended paragraph which specifically recites additional SEQ ID NOS:2-10, representing the amino acid sequences of human perlecan, endorepellin, and endorepellin fragments Δ1-Δ7 cited in the specification and claims as filed. In addition, the amino acid sequences of perlecan (SEQ ID NO:2), endorepellin (SEQ ID NO:3) and endorepellin fragments Δ1-Δ7 (SEQ ID NOS:4-10) have been added to an amended Sequence Listing which accompanies this response. Support for inclusion of the amino acid sequences and the amended Sequence Listing can be found throughout the specification, particularly in Fig. 1f. Further support for addition of the sequences is found in Fig. 2 of Murdoch et al. (J. Biol. Chem. 1992, 267:8544), which is cited throughout the specification as filed. The inventor, Dr. Renato Iozzo, verifies in his Declaration submitted herewith that the perlecan amino acid sequence now included as SEQ ID NO:2 is the same perlecan amino acid sequence which his research group published in Murdoch et al. (J. Biol. Chem. 1992, 267:8544). Dr. Iozzo also verifies in the Declaration that the amino acid sequence of the domain V/endorepellin fragment (amino acids 3687 to 4391) of perlecan, as well as all other fragments recited in the application, are derived from the perlecan sequence published in Murdoch et al., (J. Biol. Chem. 1992, 267:8544).

Support for addition of the phrase "having angiogenesis-inhibiting activity" to claim 15 can be found at page 12, lines 23-32, page 13, lines 1-7, page 15, lines 5-10 and 30-34, page 16, line 24 to page 17, line 4, and in Figs. 1c, 1f, 1g, 2b-2d, 3a-d, 4, and 5. The phrase "amino acid residues 3687 to 4391 of perlecan" in claim 15 has been amended to "amino acid residues 3687 to 4391 (SEQ ID NO:3) of perlecan (SEQ ID NO:2)." Claim 15 has also been amended to recite "wherein said endorepellin fragment comprises amino acid residues

4182 to 4391 (SEQ ID NO:10) of perlecan." Support for this amendment can be found in Figs. 1f and 1g. Dependent claim 18 has been added to recite the endorepellin fragment Δ6 (amino acid residues 4108 to 4391 of perlecan; SEQ ID NO:9). Dependent claim 19 has been added to recite the endorepellin fragment Δ7 (amino acid residues 4182 to 4391 of perlecan; SEQ ID NO:10), also called LG3. Support for addition of endorepellin fragments Δ6 and Δ7 to new claims 18 and 19, respectively, can be found in Figs. 1f and 1g and page 19 of the specification.

The amendment is discussed more fully below.

Applicant notes that the Examiner has withdrawn the indefiniteness rejection under 35 U.S.C. § 112, second paragraph, the anticipation rejection as to Murdoch et al. under 35 U.S.C. § 102(b), and the enablement rejection as to in vivo assays under 35 U.S.C. § 112, first paragraph.

Response to Rejection of Claims 15 and 17 under 35 U.S.C. § 112, first paragraph, written description

The rejection of claims 15 and 17 for lack of written description has been maintained for reasons of record. The Examiner admits that a number of examples of "fragment" corresponding to endorepellin have been disclosed in the specification. Examiner asserts at page 2 of the Office Action that there are numerous possible fragments which fall within the scope of the term "fragment," including those without functional activity. The Examiner asserts that "one of skill in the art would not readily be able to screen for such fragments because there are numerous possible fragments that fall within the scope of the term "fragment", irregardless of whether or not the fragment actually retained functional activity." The Examiner alleges that the claims lack specific functional limitations associated with the fragments, and therefore, the seven fragments disclosed in Fig. 1f are not representative of the "functional" fragments claimed. The Examiner also alleges that the claims do not reflect fragments which define a specific type of activity so as to be entitled to the broad recitation of any and all fragments of endorepellin. It is also asserted by the Examiner that the structure of the fragments is not known and that the function has not been claimed, therefore, the one of ordinary skill in the art would not know that the applicant was in possession of fragments that are representative of the fragments claimed.

Claim 17 has been cancelled herein, therefore the rejection as to this claim is now moot.

Although not necessarily agreeing with the reasoning of the Examiner, the phrase "endorepellin fragment" of independent claim 15 has been amended to "endorepellin fragment having angiogenesis-inhibiting activity." Therefore, the recited endorepellin fragment must have the function of angiogenesis-inhibiting activity. Additionally, the specification has been amended to recite specific SEQ ID NOS for perlecan, endorepellin, and endorepellin fragments. Furthermore, the amino acid sequences corresponding to each SEQ ID NO are provided in an amended Sequence Listing. Applicant respectfully submits that the specification as amended provides adequate written description of the function and structure of the claimed endorepellin fragments.

As outlined in MPEP § 2163, a description need only describe in detail that which is new or not conventional. See *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 USPQ 81, 94; *Fonar Corp. v. General Electric Co.*, 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805.

The written description requirement is viewed in light of the state of the art and skill of the practitioner at the time the application was filed. *Vas-Cath, Inc. v. Mahurkar,* 19 USPQ2d 1111 (Fed. Cir. 1991). The *Vas-Cath* Court, in a unanimous opinion, set forth the standard for the written description requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . . The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."

Vas-Cath, 19 USPQ2d at 1117 (emphasis added) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). *Accord University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). Therefore, it is well-settled that the knowledge of those skilled in the art informs the written description inquiry.

> In determining the sufficiency of support in a disclosure with respect to the written description requirement,

> "it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him." *In re Edwards*, 196 USPQ 465, 467 (C.C.P.A. 1978) (citing *In re Lukach*, 169 USPQ 795 (C.C.P.A. 1971); *In re Driscoll*, 195 USPQ 434 (C.C.P.A. 1977)).

In *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996), the court of Appeals for the Federal Circuit pointed out that literal support is not required in order to satisfy the written description requirement:

> If a person ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. For example, in *Ralston Purina Co. v. Far-Mor-Co., Inc.*, 227 USPQ 177, 180 (Fed. Cir. 1985), the trial court admitted expert testimony about known industry standards regarding temperature and pressure in "the art of both farinaceous and proteinaceous vegetable materials." The effect of the testimony was to expand the breadth of the actual written description since it was apparent that the inventor possessed such knowledge of industry standards of temperature and pressure at the time the original application was filed. (Emphasis added).

Therefore, it is clear that the invention need not be described in *ipsis verbis, i.e.*, literally, for purposes of the written description requirement under 35 U.S.C. §112, first paragraph. Rather, what is needed is that the skilled artisan understand, based upon the disclosure in the specification as filed and the knowledge imputed to the skilled artisan at the time the specification was filed, that the inventor had possession of the claimed subject matter.

More recently, in *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) cert. denied, 523 U.S. 1089 (1998), the Court of Appeals for the Federal Circuit stated:

> "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that

> the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus."

The court reasoned that factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; MPEP 2163 II(A)(3)(a)(i).

When species of a genus are claimed, only a representative number of species must be adequately described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Furthermore, the description of a representative number of species does not require the description to be of such specificity that it need provide individual support for each species of a genus. *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

The Examiner has the burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. MPEP 2163. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96.

Applicant respectfully submits that one of ordinary skill in the art, upon reading the specification, Sequence Listing, and claims as amended, would understand that the invention encompassed an endorepellin protein and biologically active fragments of endorepellin having angiogenesis-inhibiting activity. As described above, endorepellin protein (domain V of perlecan) and seven specific fragments of domain V/endorepellin are disclosed in the specification as filed (see Figs. 1f and 1g). The specification as filed also references the article disclosing the amino acid and nucleic acid sequences of human perlecan (Murdoch et al., J. Biol. Chem. 1992, 267:8544). Furthermore, Figures 1f and 1g of the specification describe specific fragment lengths and positions of the amino acid residues for the amino

and carboxy termini for endorepellin and each of the seven fragments of endorepellin disclosed in the application, relative to the perlecan sequence (SEQ ID NO:2) of Murdoch.

The specification provides human endorepellin fragments which have endorepellin activity and methods to identify such fragments. For example, the specification discloses that endorepellin and two of the deletion fragments of endorepellin, Δ1 and Δ5, comprising fragments a.a. 3687-4181 (SEQ ID NO:4) and a.a. 3927-4181 (SEQ ID NO:8), respectively, possess endostatin binding activity (page 19, lines 11-24; Fig. 1f, Fig. 1g.). As disclosed in the specification, endostatin is a novel interacting partner for endorepellin (page 18, line 14 to page 21, line 24). Thus, the Δ1 and Δ5 fragments of endorepellin have the endorepellin activity of binding to endostatin. Also as described above, the nucleic acid and amino acid sequences for perlecan were known to those of ordinary skill in the art at the time the application was filed (Murdoch et al., J. Biol. Chem. 1992, 267:8544).

Further evidence that endorepellin fragments have endorepellin activity is provided in the Iozzo Declaration. Specifically, Dr. Iozzo provides data demonstrating that endorepellin fragment Δ7 (SEQ ID NO:10; amino acid residues 4182 to 4391 of human perlecan), also called LG3, has angiogenesis-inhibiting activity as determined in several assays. As outlined in the Iozzo Declaration, endorepellin fragment Δ7 was found to inhibit branching morphogenesis (tube formation) of vascular endothelial cells and to disrupt cytoskeletal proteins in vascular endothelial cells. To that end, claim 15 has been amended by adding the phrase "wherein said endorepellin fragment comprises amino acid residues 4182 to 4391 (SEQ ID NO:10) of perlecan." Thus, claim 15 now recites an endorepellin fragment which encompasses a region of endorepellin shown to inhibit angiogenesis.

Furthermore, new dependent claim 18 recites the endorepellin fragment Δ6, which is amino acid residues 4108 to 4391 of perlecan (SEQ ID NO:9). Thus, the amino acid sequence of endorepellin fragment Δ6 also comprises the sequence of endorepellin fragment Δ7, which is shown in the Iozzo Declaration to have angiogenesis-inhibiting activity. Dependent claim 19 has been added to recite endorepellin fragment Δ7.

The specification also provides relevant molecular and biochemical methods for preparing endorepellin protein and endorepellin fragments, including specific fragment descriptions defined by residue number and by function, as well as multiple assays with which to test the ability of endorepellin protein and endorepellin fragments to inhibit

angiogenesis (see pages 3-25). A variety of in vitro and in vivo assays are provided to test anti-angiogenesis activity, such as endothelial cell migration, cell adhesion, endostatin binding, tube formation (branching morphogenesis), and vascularization assays (page 10, line 14 to page 12, line 2, and page 18, line 13 to page 22, line 24). Endothelial cell migration, cell adhesion, endostatin binding, tube formation, and vascularization are all hallmarks of angiogenesis. Thus, not only are specific structural elements of endorepellin and endorepellin fragments described, but functional activities and assays to measure functional activity of endorepellin fragments relevant to the inhibition of angiogenesis are described as well. As discussed above, only a representative number of fragments need be described to provide support for other fragments (*Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993); *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)). Because multiple fragments of endorepellin, their structures, and a variety of methods to prepare and test the activity of endorepellin fragments are disclosed in the specification, Applicant asserts that the written description is commensurate in scope to endorepellin fragments with angiogenesis-inhibiting activity as claimed in amended independent claim 15 and new dependent claims 18 and 19.

Based upon the disclosure in the specification as filed and the knowledge imputed to the skilled artisan at the time, a skilled artisan would indeed understand that the applicant had possession of the claimed subject matter, i.e., endorepellin fragments having endorepellin activity. In view of the specification and claims as amended, one of ordinary skill in the art would readily understand the definition and scope of amended claims 15 and 17. Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, written description rejection.

Response to Rejection of Claim 15 under 35 U.S.C. § 102(b), anticipation

The Examiner has maintained the rejection of claim 15 under 35 U.S.C. § 102(b) as allegedly anticipated by Snow et al. (U.S. Patent No. 5,958,883; citing column 15, lines 41-49). Applicant traverses this rejection.

The Examiner alleges at page 3 of the Office Action that Snow teaches a pharmaceutical composition comprising perlecan or derivatives thereof. The Examiner alleges that the claims have not defined the exact structure of the claimed endorepellin

fragments. The Examiner further asserts that perlecan derivatives taught by Snow anticipate the claimed invention because the endorepellin fragments cannot be distinguished over derivatives of perlecan disclosed in the prior art. Applicant respectfully disagrees.

For a reference to anticipate a claim, every limitation of that claim must identically appear, either expressly or inherently, in the reference. (MPEP § 2131; *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990)). Absence of any claim element from the reference "negates anticipation." *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81, 84 (Fed. Cir. 1986); *Rowe v. Dror*, 42 USPQ2d 1550, 1552 (Fed. Cir. 1992). Here, Snow does not disclose every element of claim 15.

Amended claim 15 recites a pharmaceutical composition comprising an endorepellin protein, wherein said endorepellin consists of amino acid residues 3687 to 4391 (SEQ ID NO:3) of perlecan (SEQ ID NO:2), or an endorepellin fragment having angiogenesis-inhibiting activity, wherein said endorepellin fragment comprises SEQ ID NO:10, and a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition comprising an endorepellin protein or its fragment having anti-angiogenesis activity is useful for treating angiogenesis related diseases and disorders, such as tumor metastasis and growth.

Snow does not anticipate claim 15 because Snow does not disclose a pharmaceutical composition comprising endorepellin or endorepellin fragments having angiogenesis-inhibiting activity. Snow discloses a composition comprising mature perlecan ($\geq$ 700,000 kD) and beta-amyloid protein (β/A4) (see column 15, lines 19-40) used to induce amyloidosis in animals.

Full length perlecan cannot be considered "endorepellin" or a fragment of endorepellin. Endorepellin is a molecule consisting of only amino acids 3687 to 4391 of perlecan. Beta-amyloid protein is unrelated to perlecan or endorepellin, and cannot be considered the same as endorepellin or an endorepellin fragment. Thus, Snow does not anticipate claim 15. Moreover, any perlecan-containing composition disclosed by Snow is not a "pharmaceutical composition" within the meaning of claim 15. A pharmaceutical is defined as "a drug or medicine" (Webster's II New College Dictionary, 1995, Houghton Mifflin Company, New York). Medicines are used to treat diseases, not induce them. The composition of Snow is not used to treat a disease or disorder. It is in fact used to induce the

disease amyloidosis in animals in order to study that disease (see column 15, lines 19-40, column 27, line 41 to column 28, line 46, and Fig. 1). Because the composition of Snow is used to induce disease, it is not a pharmaceutical composition.

In addition, Snow uses acetonitrile as a component of his amyloidosis-inducing composition. A composition containing acetonitrile cannot be considered a pharmaceutically accepted carrier within the meaning of claim 15. Acetonitrile is a member of the cyanide family (column 27, lines 4-65). Furthermore, as described above, the "composition" of Snow contains β/A4 amyloid protein. The composition is used to deposit β/A4 amyloid protein in the brain. Any composition that results in β/A4 amyloid deposition on the brain is not a "pharmaceutical" composition. Therefore, Snow does not disclose a pharmaceutical composition.

Snow merely tangentially mentions the use of "derivatives" of perlecan to induce amyloidosis (column 15, lines 41-46). The perlecan "derivatives" are "peptide derived portions of the perlecan binding domain" (column 57, lines 6-11), i.e., portions of perlecan which can bind to amyloid proteins. No such perlecan peptide-derived portions of the perlecan-binding domain are disclosed by Snow, nor does Snow provide any procedures for preparing any such derivatives of perlecan. The Snow disclosure does not identify any amyloid protein binding sites in perlecan. Indeed, it appears that Snow does not even know which parts of the perlecan molecule bind to amyloid proteins. Snow merely speculates that "once we identify the high affinity binding domain of perlecan . . . which binds to each of the different amyloid proteins described above, we can use peptide derived portions of the perlecan binding domain for infusion and/or injection in these animal models" (column 57, lines 6-11). The diffuse prophetic suggestion of some unknown part of the perlecan molecule which can purportedly bind amyloid protein is hardly a teaching of endorepellin, or any fragment of endorepellin, let alone a fragment of endorepellin having anti-angiogenesis activity as claimed in the present application.

Therefore, Snow does not disclose a pharmaceutical composition comprising endorepellin or an endorepellin fragment with angiogenesis-inhibiting activity, and a pharmaceutically acceptable carrier or excipient.

The Examiner has maintained the rejection of claim 15 under 35 U.S.C. § 102(b) as allegedly anticipated by Whitelock et al. (J. Biol. Chem. 1996, 271:10079-10086). Applicant traverses this rejection.

The Examiner asserts that the exact structure of the claimed endorepellin fragments is not taught in the specification. The Examiner alleges that Whitelock anticipates the claimed invention because the endorepellin fragments cannot be distinguished over the perlecan fragments taught by Whitelock. Applicant respectfully disagrees.

As discussed above, for a reference to anticipate a claim, every element of that claim must identically appear, either expressly or inherently, in the reference.

Amended claim 15 recites a pharmaceutical composition comprising an endorepellin protein, wherein said endorepellin consists of amino acid residues 3687 to 4391 (SEQ ID NO:3) of perlecan (SEQ ID NO:2), or an endorepellin fragment having angiogenesis-inhibiting activity, wherein said endorepellin fragment comprises amino acid residues 4182 to 4391 (SEQ ID NO:10) of perlecan and a pharmaceutically acceptable carrier or excipient. As described above, the structure of perlecan, endorepellin, and endorepellin fragments as claimed can now be determined because the specification and Sequence Listing have been amended to include specific amino acid sequences for perlecan, endorepellin, and seven specific endorepellin fragments.

Whitelock doe not disclose an endorepellin fragment having angiogenesis-inhibiting activity. Whitelock discloses binding of growth factors to domain I of perlecan, such as perlecan binding to bFGF. Whitelock also discloses perlecan-bFGF complex stimulation of cell proliferation in wound healing (page 3, line 30 to page 4, line 6; page 17, line 25 to page 19, line 8; Figures 5 and 6). Whitelock further discloses that domain I of perlecan (amino terminal domain) is the site of binding of bFGF to perlecan (page 1, lines 12-16; page 3, lines 18-23). Perlecan domain I is not endorepellin. Endorepellin consists of perlecan domain V. Domain I is at the amino terminal end of perlecan, while domain V is at the carboxy end of perlecan. Whitelock does not disclose a pharmaceutical composition comprising perlecan domain V or fragments of domain V having angiogenesis-inhibiting activity. In fact, Whitelock only discloses the use of domain I of perlecan, because domain I is required for binding to bFGF and subsequent stimulation of cell proliferation (see abstract). Thus, the pharmaceutical composition of Whitelock does not, and cannot, contain

domain V of perlecan, or fragments of domain V of perlecan as claimed in the present application. Domain I of perlecan is not the same as endorepellin, or an endorepellin fragment having anti-angiogenesis activity.

Whitelock teaches away from any protein, such as endorepellin and fragments thereof, having anti-angiogenic activity. The perlecan domain I preparations of Whitelock have the effect of stimulating cell proliferation (page 3, line 30 to page 4, line 6; page 17, line 25 to page 19, line 8; Figures 5 and 6). Whitelock focuses on the adhesive properties of perlecan domain I of perlecan to treat wound healing. Stimulation of cell proliferation and adhesion to induce wound healing is contrary to the effect of endorepellin (domain V of perlecan) and its fragments in inhibiting the adhesion of endothelial cells and subsequently the migration of endothelial cells to form new blood vessels.

Applicant submits that claim 15 as amended is not anticipated by Whitelock and requests that the rejection be withdrawn.

Response to Rejection of Claims 15 and 17 under 35 U.S.C. § 112, first paragraph, enablement

Examiner has issued a new rejection of claims 15 and 17 under 35 U.S.C. § 112, first paragraph for lack of enablement. Examiner alleges that the endorepellin sequence is improperly incorporated by reference to Murdoch et al. (J. Biol. Chem. 1992, 267:8544). The Examiner asserts that the disclosure must be amended to include the material incorporated by reference to the Murdoch publication, i.e., the endorepellin sequence.

Claim 17 has been cancelled herein, therefore the rejection as to claim 17 is now moot.

Although not necessarily agreeing with the reasoning of the examiner, Applicant has amended the Sequence Listing (submitted herewith) by adding the sequence of perlecan (new SEQ ID NO:2) as disclosed in Murdoch et al. (J. Biol. Chem. 1992, 267:8544) and adding the sequences of the fragment of perlecan referred to as endorepellin (new SEQ ID NO:3), as well as the sequences of the fragments of endorepellin disclosed in the application as filed (new SEQ ID NOS:4-10).

The specification has been amended by replacing the paragraph at page 19, lines 11-24 with an amended paragraph which specifically recites additional SEQ ID NOS:2-10,

representing the amino acid sequences of perlecan, endorepellin, and fragments Δ1-Δ7 cited in the specification and claims as filed. In addition, the amino acid sequences represented by SEQ ID NOS:2-10 have been added to an amended Sequence Listing which accompanies this response. Support for inclusion of the amino acid sequences and the amended Sequence Listing can be found throughout the specification, particularly in Fig. 1f.

The Examiner has requested a declaration indicating that the proposed amendment which adds sequences and SEQ ID NOS is the same subject matter that was referenced from Murdoch et al. (J. Biol. Chem. 1992, 267:8544). The Iozzo Declaration submitted herewith verifies that the perlecan amino acid sequence now included as SEQ ID NO:2 is the same perlecan amino acid sequence which his research group published in Murdoch et al. (J. Biol. Chem. 1992, 267:8544). The Declaration also verifies that the amino acid sequence of the domain V/endorepellin fragment (amino acids 3687 to 4391; new SEQ ID NO:3) of perlecan, as well as all other endorepellin fragments recited in the application as filed and in the amended specification and Sequence Listing (new SEQ ID NOS:4-10), are derived from the perlecan sequence published in Murdoch et al., (J. Biol. Chem. 1992, 267:8544).

Applicant submits that amended claim 15, as well as new dependent claim 18 and 19, are enabled and request that the rejection be withdrawn.

Response to Rejection of Claims 15 and 17 under 35 U.S.C. § 103(a), obviousness

The Examiner has issued a new rejection, alleging that claims 15 and 17 are unpatentable over Friedrich et al. (J. Mol. Biol. 1999 294:250-270), in view of Snow.

The Examiner asserts that Friedrich discloses amino acid sequences identical to amino acids 3687-4391 (endorepellin) as recited in claim 15, and to amino acids 3927-4181 as recited in claim 17 (citing page 260, paragraph 1 and Fig. 1). The Examiner alleges that endorepellin appears to be the same molecule as domain V of perlecan taught by Friedrich. The Examiner asserts that although Friedrich does not disclose a compound in combination with a pharmaceutical carrier, it would be obvious to do so in view of Snow. The Examiner also alleges that Snow teaches the use of biologically active perlecan fragments in a pharmaceutical carrier. The Examiner then alleges that it would have been obvious to one of skill in the art to use fragments of domain V or endorepellin in a pharmaceutical carrier

for administration to a subject, because it was taught that domain V (endorepellin) and its fragments are involved in diverse biological functions.

The Examiner asserts that one of skill in the art would have been motivated to combine the fragments of domain V (endorepellin) with a pharmaceutical carrier because Friedrich demonstrated that the fragments have biological activity (citing pages 260-265 and Fig. 7). The Examiner further alleges that the combination of domain V (endorepellin) and/or a fragment consisting of 3927-4181 with a pharmaceutical carrier is obvious absent any unexpected results. Applicant traverses this rejection.

Claim 17 has been cancelled herein, therefore the rejection as to this claim is now moot.

Applicant respectfully submits that the combination of Friedrich and Snow does not render claim 15 *prima facie* obvious under 35 U.S.C. § 103(a) for the following reasons.

Preliminarily, the three-prong test which must be met for a reference or a combination of references to establish a prima facie case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

To support a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. *In re Dow Chemical Company*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). None of these criteria have been met here.

It would not have been obvious to combine Friedrich and Snow. Even if combined, the result is not the claimed invention. Friedrich describes a study where overlapping fragments of mouse perlecan domain V were prepared by recombinant production in mammalian cells to map the glycosaminoglycan (GAG) substitution site on perlecan, and

the binding sites of several carbohydrate and protein ligands (Table 1). [1] The abstract, based on results using mouse domain V, concludes that "a complex modular structure is required for domain V in order to provide a rich repertoire of potential biological functions."

Furthermore, as recognized by the Examiner, Friedrich does not disclose combining domain V from any species with a pharmaceutical carrier. The reason is clear. The observations of Friedrich into the structure of perlecan domain V, no matter how extensive, do not teach or suggest any discrete pharmaceutical utility for that molecule, or any fragments thereof.

As described above, Snow teaches animal models of amyloidosis induced by co-administration of β/A4 amyloid protein with mouse perlecan, or yet to be defined "derivatives thereof" (column 15, line 46). There is nothing in Snow to associate these "derivatives" of perlecan with domain V of that molecule, or any fragment of domain V. Furthermore, Snow teaches away from a pharmaceutically useful composition. The principal component of Snow's composition is β/A4 amyloid protein, which is used to cause disease (amyloidosis), not treat disease. Neither Friedrich nor Snow teach or suggest a pharmaceutical utility for human endorepellin or endorepellin fragments. Because neither Friedrich nor Snow teaches a pharmaceutical use for these molecules, there would have been no incentive to prepare a pharmaceutical composition.

Because it would not have been obvious to combine Friedrich with Snow, and because the combination does not result in all elements of the claimed invention, the combination of these references does not render *prima facie* obvious the invention as claimed. Thus, the rejection of independent claim 15 under 35 U.S.C. § 103(a) should be withdrawn.

[1] Mouse and human domain V are not homologous (Friedrich, Figure 9). For example, the LG3 region of mouse domain V used by Friedrich differs from the human LG3 region of endorepellin/domain V (also referred to as Δ7, in the application) at 11 of 42 (26%) amino acid positions (Friedrich, Figure 9).

Conclusion

Based on the foregoing, amended claim 15 and its new dependent claims, 18 and 19, are believed to be in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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